

## High Rate of Microbleed Formation Following Primary Intracerebral Hemorrhage

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Search terms: intracerebral hemorrhage [7], cerebral microbleeds, MRI imaging [120]

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**Abstract:**

**Introduction:** We sought to investigate the frequency of microbleed (MB) development following intracerebral hemorrhage (ICH) in a predominantly African-American population and to identify predictors of new MB formation.

**Methods:** The DECIPHER study was a prospective, longitudinal, MR-based cohort study designed to evaluate racial/ethnic differences in risk factors for MBs and to evaluate the prognostic impact of MBs in this ICH population. We evaluated new MB formation in 2 time periods: from baseline to 30 days and from 30 days to year 1.

**Results:** Of 200 subjects enrolled in DECIPHER, 84 had MRIs at all required timepoints to meet criteria for this analysis. In the baseline to day 30 analysis, 11 (13.1%) had new MBs, compared to 25 (29.8%) in the day 30 to year 1 analysis. Logistic regression analysis demonstrated that baseline number of MBs (OR 1.05 [95% CI 1.01, 1.08],  $p=0.01$ ) was associated with new MB formation at 30 days. A logistic regression model predicting new MB at 1 year included baseline number of MBs (OR 1.05 [1.00, 1.11],  $p=0.046$ ), baseline age (OR 1.05 [1.00, 1.10],  $p=0.04$ ) and WMD disease score (OR 1.18 [0.96, 1.45],  $p=0.115$ ). Overall 28 of 84 (33.3%) ICH subjects formed new MBs at some point in the first year post-ICH.

**Conclusions:** We found that one-third of ICH subjects in this cohort surviving one year developed new MBs, which suggests a dynamic and rapidly progressive vasculopathy. Future studies are needed to examine the impact of new MB formation on patient outcomes.

## **Introduction:**

Cerebral microbleeds (MBs) are small, chronic, asymptomatic, perivascular hemorrhages that appear as dark round areas of signal loss detected on T2\*-weighted magnetic resonance images. MBs are increasingly recognized as markers for a hemorrhage-prone vasculopathy(1) and have been reported in up to 35% of community-dwelling elderly,(2) 30% of ischemic stroke patients, and 60% of intracerebral hemorrhage (ICH) patients.(3) MBs have been associated with increased bleeding risk in ischemic stroke(4) and ICH populations,(5, 6) and have also been associated with cognitive impairment.(7)

Evidence suggests that MB formation is a highly dynamic process, with new MBs forming shortly after ischemic stroke,(8) carotid artery stenting,(9) thrombolysis,(10) and cardiac valve surgery,(11) among other conditions; however, few studies have evaluated the rate and time course of new MB development prospectively following ICH,(5, 6) particularly in the first month. Furthermore, few studies have assessed MBs in the African-American population with predominantly hypertensive ICHs.(12) We therefore sought to investigate the frequency of rapid MB development and to identify predictors of new MB formation in this population.

## **Methods:**

The Differences in the Imaging of Primary Hemorrhage Based on Ethnicity or Race (DECIPHER) study was a prospective, longitudinal, MR-based cohort study designed to evaluate racial/ethnic differences in risk factors for MBs and to evaluate the prognostic impact of MBs in underserved, predominantly African-American subjects with ICH. Subjects were recruited from five Washington, DC hospitals from 2007-2012. For inclusion in the study, subjects had to be 18

years of age or older and diagnosed with a primary ICH. Subjects who were pregnant, unable to undergo an MRI, or diagnosed with a CNS tumor, active infectious or inflammatory process such as encephalitis, AVM, or aneurysm were excluded. Subjects were also excluded if they had CNS trauma within the previous two weeks, a craniotomy, or an INR>3. Baseline demographics, vascular risk factors, medications, laboratory data, and neurological assessments were obtained for each subject. Follow-up MRIs were performed at day 30 and year 1 following initial ICH.

The general imaging analysis performed in the DECIPHER study has been described previously.<sup>(13)</sup> For inclusion in the present study subjects had to have usable gradient recalled echo (GRE) images (1.5 or 3T; repetition time, 46 to 825 ms; echo time, 12 to 30.5 ms; flip angle, 20 to 40 degrees; and slice thickness, 3.5 to 7 mm) at baseline, 30 days from onset, and 1 year from onset. Figure 1 demonstrates a flow chart for subject inclusion for the present study in the setting of the larger DECIPHER cohort. Sequence parameters were provided to each of the sites to optimize standardization of the gradient echo protocol across hospitals; in addition, the vast majority of day 30 and year 1 images were performed on a single scanner. We evaluated new MB formation in two time periods: from baseline to day 30 and from day 30 to year 1. Day 30 and year 1 images were co-registered to the baseline images using MIPAV (Medical Image Processing, Analysis, and Visualization, <http://mipav.cit.nih.gov/>). Blinding of imaging time-point was not possible because of the appearance of the primary ICH, which has distinct characteristics at each timepoint. Hypointensities in the sulci consistent with vessels and symmetric hypointensities in the basal nuclei thought to represent calcification were not considered MBs. Hypointensities closely adjacent to or contiguous with the primary ICH were not considered MBs. MB presence and location at all three timepoints were determined by

consensus review by two stroke neurologists with imaging expertise. White matter disease (WMD) score was determined via a modified Fazekas method(14) with a score of 0 to 3 on each side for both the periventricular and deep white matter regions (maximum score of 12). The covariates of hyperlipidemia, diabetes, prior TIA or stroke, history of antithrombotic use, smoking history, atrial fibrillation coronary artery disease, and statin use were obtained at baseline via history. Mean arterial pressure in mmHg was obtained at baseline, 30 days, and 1 year. ApoE status was stratified by  $\epsilon 3/\epsilon 3$  vs.  $\epsilon 2/--$  or  $\epsilon 4/--$ . Socioeconomic status was dichotomized by middle to upper status vs. lower to lower-middle status using a combination of occupation and education to generate the Hollingshead two factor index of social position.(15)

### Statistical Methods

Univariate analyses were performed for both time intervals using chi-square, Fisher's exact, Student's t, or Wilcoxon rank sum tests where appropriate. Logistic regression analysis was performed for both time periods with new MB formation as the outcome variable. Variables that were borderline statistically significant ( $p \leq 0.10$ ) in the univariate analyses were considered for inclusion as predictors in the logistic regression model. Statistical analyses were performed with SAS version 9.3 (SAS institute, Cary NC).

### IRB approval/general statement

The IRBs of the five study hospitals approved the DECIPHER study; Georgetown University served as the IRB of record.

### **Results:**

Of the 200 subjects enrolled in DECIPHER, 84 subjects had MRIs at all three timepoints and thus met criteria for this subset analysis; 42.9% were women and 78.6% were African-American. The mean age was 58.0 years (SD 13.6). The median baseline NIHSS score was 4 (IQR 2-10). The median ICH volume was 11.4 mL (IQR: 4.9-29.7) and mean volume was 18.2 mL (SD 17.2). ICH location was deep in 72.6% and 81% of subjects had a history of hypertension.

#### Baseline – day 30 analysis

Of 84 subjects, 11 (13.1%) developed new MBs by day 30. The univariate analysis dichotomizing subjects into new MBs and no new MBs is shown in Table 1. Aside from the number of baseline MBs and prior TIA/stroke, there were no significant differences between groups in terms of demographics, vascular risk factors, or ICH characteristics. There were no significant differences between the groups with regard to apoE status, smoking, atrial fibrillation, hyperlipidemia, or coronary artery disease (data not shown).

#### Multivariable analysis

The predictors of new MB formation considered for the model were age, baseline number of MBs, diabetes, and prior TIA/stroke. Simple logistic regression analysis demonstrated that for a one unit increase in number of baseline MBs, the odds of having a new MB at day 30 increased by 5% (OR 1.05 [95% CI 1.01, 1.08],  $p=0.01$ ).

#### Day 30 – year 1 analysis

Of 84 subjects in this analysis, 25 (29.8%) developed new MBs between day 30 and year 1. The univariate analysis dichotomizing subjects into new MBs and no new MBs is shown in Table 2.

Subjects developing new MBs at 1 year were older, had higher WMD scores, more MBs at 30 days, higher mean arterial pressures (MAPs) at 1 year, and were more likely to have had a prior TIA/stroke. There was a trend toward more diabetes and lower socioeconomic status in the new MBs group. Again, there were no significant differences between the groups with regard to apoE status, smoking, atrial fibrillation, hyperlipidemia, or coronary artery disease (data not shown). An example of new MB formation at 1 year is shown in Figure 2.

### Multivariable analysis

The predictors of new MB formation considered for the model were age, WMD score, baseline number of MBs, MAP, diabetes, prior TIA/stroke, and socioeconomic status. Our final logistic regression model included age, baseline number of MBs, and WMD. This model demonstrated that for a one unit increase in the number of MBs, the odds of having a new MB at year 1 increased by 5% (OR 1.05 [95% CI 1.00, 1.11],  $p=0.05$ ). Similarly, a one year increase in age increased the odds of having a new MB at year 1 by 5% (OR 1.05 [1.00, 1.10],  $p=0.04$ ).

Although the association between WMD and new MBs at year 1 did not meet statistical significance, we included it in the model; in this model, a one unit higher WMD score increased the odds of having a new MB at year 1 by 18% (OR 1.18 [0.96, 1.45],  $p=0.12$ ).

Overall 28 of 84 (33.3%) ICH subjects formed new MBs at some point in the first year post-ICH. In a subset analysis of subjects with only 3T MRI GRE images at all three time points, 12 of 39 (30.8%) formed new MBs at any time point. The location of MBs at baseline stratified by index ICH location is shown in Table 3. Index cerebellar and brainstem ICHs were categorized as deep. There were 43 subjects (51.2%) with MBs at baseline; there were no significant differences

between the deep and lobar ICHs with regard to MB location (Fisher exact=0.33). Table 4 shows the location of incident MBs stratified by index ICH location. Most incident MB formation in the first 30 days occurred in the lobar region. We did not observe a clear pattern of location of incident MB formation based on index ICH location.

### **Discussion:**

In this predominantly hypertensive African American population, we found that one-third of ICH subjects who survived one year developed new MBs and that baseline number of MBs and age are independently associated with new MB formation. Our study also supports previous studies demonstrating that new MB formation is associated with higher WMD scores. Our study uniquely quantifies the relatively rapid rate of MB development over the first year following a primary ICH in a systematic and prospective study.

Prospective studies of new MB formation in ICH subjects are relatively sparse. Investigators in Boston evaluated new MB formation in a predominantly white population with lobar ICH and found that 17 of 34 (50%) subjects undergoing follow-up imaging at approximately 16 months had new MBs.<sup>(5)</sup> Investigators in Korea found that 19 of 63 (30%) subjects undergoing repeat imaging at a median of 23 months developed new MBs.<sup>(6)</sup> Neither of these studies evaluated MB formation shortly after ICH. Thirteen percent of subjects in our study developed new MBs by day 30, which suggests that some subjects may be at particularly high risk for appreciable progression of vasculopathy in the period immediately following ICH.



Histopathologic work has demonstrated that MBs noted on GRE sequences represent hemosiderin-laden macrophages adjacent to small vessels.(16) While small vessel angiopathies due to hypertensive disease or cerebral amyloid angiopathy are thought to play critical roles, the mechanisms of MB formation and the triggering factors are not entirely clear. Extravasation of blood due to blood-brain barrier disruption may be due to several inter-related factors, including endothelial dysfunction, active inflammation, and loss of autoregulation, all of which are common in the immediate period following ICH. A large cohort study has found that risk factors for MB formation include advancing age, cardiovascular risk factors for deep MBs, and apolipoprotein E4 for strictly lobar MBs.(2) Baseline MBs,(8) African-American race(12) and chronic kidney disease(17) have also been associated with MB formation. A recent longitudinal study has also found that blood pressure variability in patients with recent ischemic stroke was associated with MB progression.(18)

In this study, we found that WMD score may be associated with new MB formation at 1 year in ICH subjects, though this did not reach statistical significance. WMD has previously been associated with new MB formation following ischemic stroke(8) and has also been associated with new DWI lesion formation in ICH subjects.(19, 20) Emerging evidence suggests that a widespread vasculopathic process accompanies the peri-ICH period, and several groups have reported DWI-positive lesions shortly after ICH(13, 19-23) and even one year after the index hemorrhage.(24) A dynamic interplay between new ischemic lesions and MBs(25) may be occurring. One possible explanation for differing lesion types is that the peri-ICH environment leads to very fragile vessels in which relative hypotension may predispose to an ischemic event

and relative hypertension to a microhemorrhage in the setting of compromised microstructural integrity.(26)

The present work is the largest prospective study of MBs in a predominantly African-American cohort and is the first study to evaluate new MB formation in the first month following ICH. This study builds upon the work demonstrating rapid new MB formation following ischemic stroke by extending similar findings to ICH. Additional strengths of this work are co-registration of images to prevent misclassification and standardized imaging timepoints. There are also several limitations to this study. DECIPHER was not designed to be a population-based study and the results of this analysis might not be generalizable to the population as a whole, though it provides novel and important data in an underserved population. The sample size of subjects who formed new MBs was somewhat small, particularly in the baseline to day 30 analysis. The sample size also limited the number of predictor variables in the multivariable model.(27)

Inclusion of 3T and 1.5T MRI increases the possibility of bias as higher field strength is associated with improved MB detection.(28) We also did not perform blinded individual reads of the images. We instead relied on a consensus review of the co-registered images together to reduce ‘overcall’ of new MB formation. Finally, ascertainment bias is a concern because inclusion in the study required subjects being well enough to undergo an MRI without significant motion artifact at three different time points.

Rapid MB formation following ICH suggests an ongoing dynamic and rapidly progressive vasculopathy in these subjects. Further prospective work with larger samples will more fully evaluate risk factors for new MB formation and examine the impact of new MB formation and

location on patient outcomes. Much additional work is also needed to identify interventions to arrest the vasculopathic process.

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### **Conflicts of Interest**

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Table 1: Baseline – day 30 characteristics

	<b>New MBs (n=11)</b>	<b>No new MBs (n=73)</b>	<b>p-value</b>
Age (mean, SD)	63.8 (11.5)	57.1 (13.7)	0.10
Female	5 (45%)	31 (42%)	0.99

Race (black)	7 (64%)	59 (81%)	0.24
WMD score, median (IQR)	8 (6-10)	6 (4-10)	0.15
ICH volume, mL (MRI)	5.4 (3.3-31.0)	11.8 (5.5-29.2)	0.13
Baseline no. of MBs, median (IQR)	17 (3-61)	0 (0-5)	0.002
MAP at outcome timepoint (mmHg, SD)	104 (14)	99 (13.6)	0.38
ICH location (baseline MRI)			0.48
Lobar	4 (36%)	19 (26%)	
Deep	7 (64%)	54 (74%)	
Diabetes	4 (36%)	11 (15%)	0.10
Prior TIA/stroke	7 (64%)	15 (21%)	0.01
SES (middle or higher)	6 (55%)	38* (53%)	0.91
Antithrombotic at baseline	4 (36%)	19 (26%)	0.48
Statin use at baseline	3 (27%)	10 (14%)	0.36

\*One subject missing SES data

Table 2: Day 30 – year 1 characteristics

	<b>New MBs (n=25)</b>	<b>No new MBs (n=59)</b>	<b>p-value</b>
Age (mean, SD)	65.1 (13.3)	54.9 (12.6)	0.002
Female	10 (40%)	26 (44%)	0.73
Race (black)	21 (84%)	45 (76%)	0.43
WMD score, median (IQR)	8 (7-10)	5 (4-8)	<0.001
ICH volume, mL	7.9 (3.4-22.5)	11.8 (5.2-33.5)	0.23
Baseline no. of MBs, median (IQR)	8 (0-18)	0 (0-2)	0.001
MAP at outcome timepoint (mmHg, SD)	113 (23)	100 (18)	0.04
ICH location (baseline MRI)			0.54
Lobar	8 (32%)	15 (25%)	
Deep	17 (68%)	44 (75%)	

Diabetes	8 (32%)	7 (12%)	0.06
Prior TIA/stroke	11 (44%)	11 (19%)	0.02
SES (middle or higher)	9* (38%)	35 (59%)	0.07
Antithrombotic at day 30	9 (36%)	14 (24%)	0.25
Statin use at day 30	3 (12%)	10 (17%)	0.75

\* One subject missing SES data

Table 3: Microbleed location at baseline stratified by ICH location

	No MBs at baseline	Only deep MBs	Only lobar MBs	Deep and lobar MBs
Deep ICH	27 (44.3%)	8 (13.1%)	6 (9.8%)	20 (32.8%)
Lobar ICH	14 (60.9%)	0	2 (8.7%)	7 (30.4%)

Note: 'Deep' includes cerebellum and brainstem

Table 4: Location of new microbleed formation in relation to primary ICH location

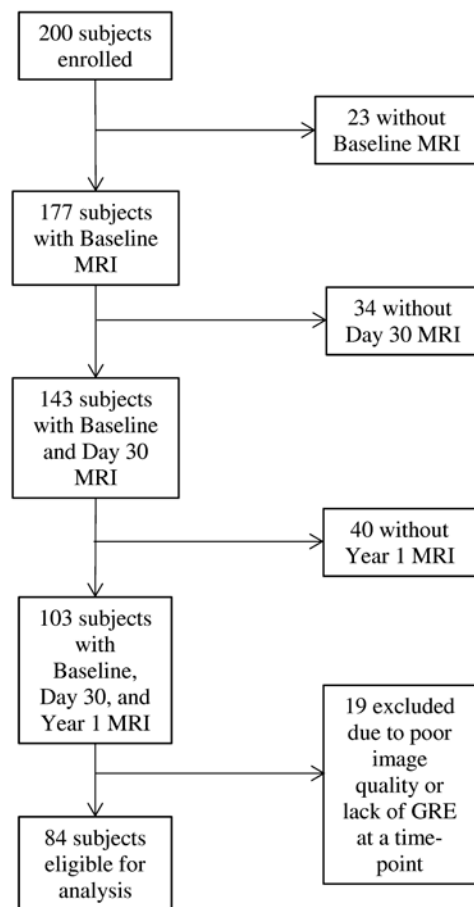
	New deep MBs	New lobar MBs	New deep and lobar MBs
Day 30			
Deep ICH	0	7	0
Lobar ICH	1	2	1
1-year			
Deep ICH	5	5	7
Lobar ICH	4	3	1

Note: 'Deep' includes cerebellum and brainstem

**Figure 1:** Flowchart demonstrating exclusions from the overall DECIPHER cohort

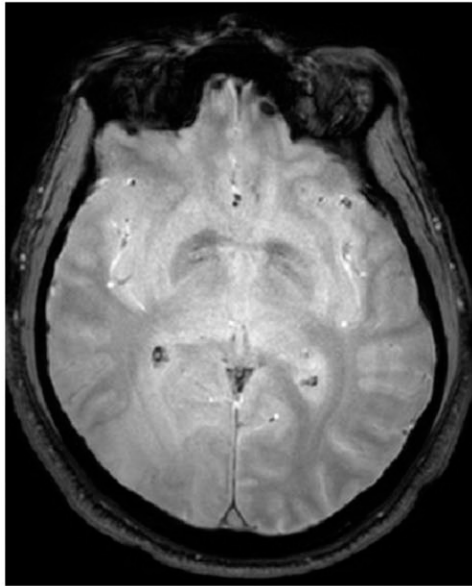
**Figure 2:** Axial gradient recalled echo images from day 30 and year 1 demonstrating new microbleed formation at year 1.

**Fig.1** Flowchart demonstrating exclusions from the overall DECIPHER cohort.

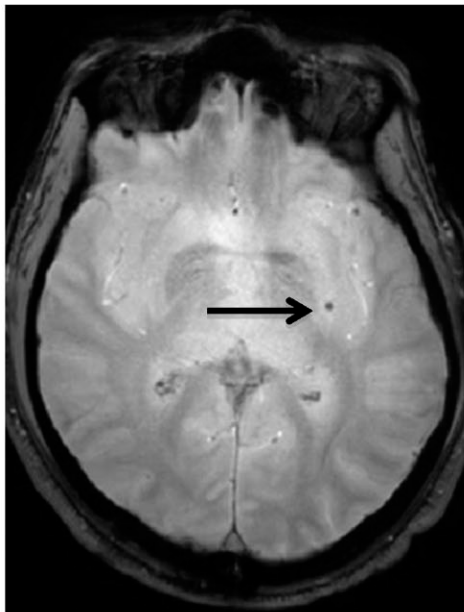




**Fig. 2** Axial gradient recalled echo images from day 30 and year 1 demonstrating new microbleed formation at year 1.



Day 30



Year 1